

This listing of claims will replace all prior versions, and listings, of claims in the application:

In the claims:

Claim 1 (withdrawn): A non-human transgenic animal whose germ cells and somatic cells contain a knockout mutation in the endogenous $ERR\alpha$ orphan nuclear receptor gene, and wherein said transgenic animal shows a phenotype of an altered fat and/or glucose metabolism as compared to a control animal.

Claim 2 (withdrawn): The transgenic animal of claim 1, wherein said germ cells and somatic cells contain a homozygous disruption of said $ERR\alpha$ gene, and wherein said disruption comprises the insertion of a selectable marker sequence.

Claim 3 (withdrawn): The non-human transgenic animal of claim 1, wherein said animal is a mammal.

Claim 4 (withdrawn): The non-human transgenic animal of claim 3, wherein said animal is a mouse.

Claim 5 (withdrawn): The non-human transgenic animal of claim 1, displaying a lean phenotype.

Claim 6 (withdrawn): The non-human transgenic animal of claim 1, whose germ cells and somatic cells additionally comprise a transgene encoding a non endogenous $ERR\alpha$ orphan nuclear receptor gene, wherein said transgene is expressed at levels sufficient to complement the disrupted endogenous $ERR\alpha$ orphan nuclear receptor activity.

Claim 7 (withdrawn): The non-human transgenic animal of claim 6, wherein said non endogenous $ERR\alpha$ orphan nuclear receptor gene is a human $ERR\alpha$ orphan nuclear receptor gene.

Claim 8 (withdrawn): The non-human transgenic animal of claim 7, wherein said animal is a mouse and said non-endogenous $ERR\alpha$ is a human $ERR\alpha$ gene.

Claim 9 (withdrawn): A cell line derived from the non-human transgenic animal of claim 1.

Claim 10 (withdrawn): A method of producing a non-human transgenic animal, in which at least some cells thereof contain an altered gene encoding an altered $ERR\alpha$, said altered gene having been targeted to disrupt the endogenous $ERR\alpha$ gene in said transgenic animal, said method comprising:

- a) providing an altered gene encoding the altered form of $ERR\alpha$ and designed to target and disrupt said endogenous $ERR\alpha$ gene of an embryonic stem cells (ES) of said animal;
- b) introducing said altered gene in said ES cells;
- c) selecting ES cells in which said altered $ERR\alpha$ gene has disrupted said endogenous $ERR\alpha$ gene;
- d) injecting said selected ES cells of c) into blastocysts;
- e) implanting said blastocysts of d) in a pseudopregnant animal; and
- f) producing a non-human transgenic animal having at least some cells having said altered $ERR\alpha$ gene encoding said altered $ERR\alpha$.

Claim 11 (withdrawn): The method of claim 10, wherein said non-human transgenic animal is a mouse.

Claim 12 (withdrawn): A method of producing the non-human transgenic animal of claim 5, said method comprising:

(a) providing a non-human transgenic animal lacking detectable levels of $ERR\alpha$ orphan nuclear receptor gene and exhibiting a lean phenotype;

(b) introducing a non endogenous $ERR\alpha$ orphan nuclear receptor transgene encoding a functional $ERR\alpha$ orphan nuclear receptor gene into the pronucleus of a zygote derived from said animal of a), said zygote containing a homozygous disruption of the endogenous $ERR\alpha$ orphan nuclear receptor gene;

(c) transplanting said animal zygote into a pseudopregnant compatible animal;

(d) allowing said zygote to develop to term;

(e) obtaining a founder animal carrying said transgene; and

(f) breeding said founder animal with a wild-type animal to obtain progeny that express said non endogenous $ERR\alpha$ orphan nuclear receptor transgene at levels sufficient to functionally complement the disrupted $ERR\alpha$ receptor activity.

Claim 13 (withdrawn): The method of claim 12, wherein said non-human transgenic animal is a mammal.

Claim 14 (withdrawn): The method of claim 12, wherein said mammal is a mouse, and wherein said non-endogenous $ERR\alpha$ transgene is a human $ERR\alpha$ gene.

Claim 15 (currently amended): A method for screening and identifying a compound which modulates $ERR\alpha$ orphan nuclear receptor activity, the method including:

a) exposing the non-human transgenic animal of claim [[5]]8 to a candidate compound, and;

b) determining the activity of said $ERR\alpha$ orphan nuclear receptor in said animal,

wherein an increase in the receptor activity as compared to an unexposed non-human animal is indicative of a compound being capable of increasing $ERR\alpha$ orphan nuclear receptor activity, while a decrease in said receptor activity as compared to an unexposed non-human animal, is indicative of a compound being capable of decreasing $ERR\alpha$ orphan nuclear receptor activity.

Claim 16 (original): The method of claim 15, further comprising a determination of at least one parameter selected from the group consisting of: mass, body temperature, body fat content, fat to lean mass ratio, white adipose tissue deposits, basal metabolic rate, food intake, hepatic synthetic functions, fasting serum triglyceride, serum glucose levels, level of expression of uncoupling protein mRNA in brown adipose tissue (BAT) and skeletal muscle, adipocyte volume in fat pads, lipogenesis, fatty acid esterification and fatty acid oxydation.

Claim 17 (currently amended): A method of further identifying an agent which modulates fat and/or glucose metabolism *in vivo* through a modulation of $ERR\alpha$ activity and/or level comprising:

a) administering an agent suspected of being a modulator of $ERR\alpha$ activity and/or level in ~~an~~ the transgenic animal of claim 4, wherein said agent has been identified as a suspected modulator of $ERR\alpha$ activity and/or level in a previous screening assay; and

b) measuring lipid and/or glucose levels in the animal of step a) and comparing same with that of a control animal not having been administered said agent, wherein ~~and~~ no difference in lipid and/or glucose levels of the animal of step a) as compared to that of the ~~control-untreated~~ animal, further identifies said agent as a modulator of fat and/or glucose metabolism *in vivo* through a modulation of $ERR\alpha$ activity and/or level

Claim 18 (currently amended): Method of identifying an agent which modulates fat and/or glucose metabolism *in vivo* comprising:

- a) providing a promoter operably linked to a selectable or assayable marker, wherein said promoter ~~being~~ is capable of being modulated by $ERR\alpha$;
- b) measuring or ~~selecting~~ assaying for said marker in a presence and in an absence of an agent ~~suspected of modulating the promoter modulating activity of $ERR\alpha$~~ , wherein thereby identifying an agent which modulates $ERR\alpha$ activity is identified when ~~wherein~~ a difference is observed between in the transcriptional activity of said promoter in the presence of said agent, as compared to that in the absence thereof, ~~identifies said agent as a modulator of $ERR\alpha$ activity;~~
- c) administering said agent identified in b) to a non-human transgenic animal according to claim [[1]]8; and
- d) measuring and comparing lipid and/or glucose levels in said animal of step c) and ~~comparing same with that of in~~ a control animal, not having been administered said agent identified in b), wherein a difference in lipid and/or glucose levels of the animal of step c) as compared to that of said control animal identifies said agent as a modulator of fat and/or glucose metabolism *in vivo*.

Claim 19 (original): The method of claim 18, where the agent is obtained from a library of compounds.

Claim 20 (cancelled)

Claim 21 (cancelled)

Claim 22 (withdrawn): A modulator of fat and/or glucose metabolism *in vivo* identified by the method of claim 18.

Claim 23 (withdrawn): A method of modulating fat tissue growth and/or weight gain, comprising:

- a) administering to an animal an agent which modulates the promoter activity of a gene, wherein said promoter comprises cis-acting elements selected from the group consisting of:

- i) an estrogen response element;
- ii) TGA AGG TCA (SEQ ID NO:2);
- iii) AGG TCA NNN TGA CCT (SEQ ID NO:1); and
- iv) functional variants of i-iii)

such as to modulate the level of said gene, thereby modulating fat tissue growth and/or weight gain in said animal.

Claim 24 (withdrawn): The method of claim 23, wherein said agent modulates said promoter activity of said gene, by decreasing a level and/or activity of $ERR\alpha$.

Claim 25 (withdrawn): The method of claim 24, wherein said agent is an antibody specific to $ERR\alpha$, or an epitope-bearing portion thereof.

Claim 26 (withdrawn): The method of claim 23, wherein said modulation of said promoter activity is effected by inhibition of $ERR\alpha$ synthesis.

Claim 27 (withdrawn): The method of claim 26, wherein said agent comprises an antisense RNA, complementary to a nucleotide sequence encoding $ERR\alpha$.

Claim 28 (currently amended): A method of determining whether an agent modulates fat tissue growth and/or weight gain in an animal comprising:

- a) providing a transcriptionally active preparation of $ERR\alpha$, ~~or~~ $ERR\beta$, or $ERR\gamma$ related factors and a DNA sequence comprising a promoter having a cis-acting sequence ~~which modulates activity thereof by an~~ which interaction interacts thereto of with said $ERR\alpha$, $ERR\beta$, or $ERR\gamma$ and related factors;

b) measuring ~~said~~ a transcriptional activity of said promoter or ~~of~~ a binding of at least one of $ERR\alpha$, $ERR\beta$, and $ERR\gamma$ ~~or related factors~~ to said cis-acting sequence in a presence ~~and in an~~ absence of an agent suspected ~~of modulating the transcriptional activity of said promoter or the binding of said factors to said cis-acting sequence, thereby identifying, wherein an agent is selected which modulates transcription of said promoter and wherein when~~ a difference in the transcriptional activity and/or binding to said cis-acting sequence is observed in the presence of said agent, as compared to ~~that in the absence thereof identifies said agent as a modulator of transcription;~~

c) administering said agent ~~identified~~ selected in b) to a the non-human transgenic animal according to claim 1 ~~8~~; and

d) measuring and comparing fat tissue growth and/or weight gain in the animal of step c) ~~and comparing same with that of~~ in a control animal, not having been administered said agent, wherein a difference in fat tissue growth and/or weight gain of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of fat tissue growth and/or weight gain *in vivo*.

Claim 29 (original): The method of claim 28, where the agent is obtained from a library of compounds.

Claim 30 (cancelled)

Claim 31 (cancelled)

Claim 32 (withdrawn): A modulator of fat and/or glucose metabolism *in vivo* identified by the method of claim 28.

Claim 33 (withdrawn): A method of treating and/or preventing obesity, comprising administering to an obese animal, or an animal susceptible of becoming obese, an agent which

modulates the promoter activity of a promoter comprising a cis-acting element selected from the group consisting of:

- i) an estrogen response element;
- ii) TGA AGG TCA (SEQ ID NO:2);
- iii) AGG TCA NNN TGA CCT (SEQ ID NO:1); and
- iv) functional variants of i-iii)

wherein cis-acting element is capable of binding to $ERR\alpha$.

Claim 34 (withdrawn): The method of claim 33, wherein said agent reduces the level and/or activity of $ERR\alpha$.

Claim 35 (currently amended): A method of determining whether an agent modulates obesity in an animal comprising:

a) providing a transcriptionally active preparation of $ERR\alpha$, ~~or $ERR\beta$, or $ERR\gamma$ related factors~~ and a DNA sequence comprising a promoter having a cis-acting sequence ~~which modulates activity thereof by an~~ which interaction interacts thereto of with said $ERR\alpha$, $ERR\beta$, or $ERR\gamma$ ~~and related factors~~;

b) measuring ~~said~~ a transcriptional activity of said promoter ~~or of a binding of at least one of $ERR\alpha$, $ERR\beta$, and $ERR\gamma$ or related factors~~ to said cis-acting sequence in a presence ~~and in an absence of an agent suspected of modulating the transcriptional activity of said promoter or the binding of said factors to said cis-acting sequence, thereby identifying, wherein an agent is selected which modulates transcription of said promoter and wherein when~~ a difference in the transcriptional activity and/or binding to said cis-acting sequence is observed in the presence of said agent, as compared to ~~that in the absence thereof identifies said agent as a modulator of transcription~~;

c) administering said agent ~~identified~~ selected in b) to a the non-human transgenic animal according to claim 1 ~~8~~; and

d) assessing and comparing obesity in the animal of step c) and ~~comparing same with that of~~ in a control animal, not having been administered said agent, wherein a difference in obesity of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of obesity *in vivo*.

Claim 36 (original): The method of claim 35, where the agent is obtained from a library of compounds.

Claim 37 (cancelled)

Claim 38 (cancelled)

Claim 39 (withdrawn): A modulator of glucose or fat metabolism *in vivo* identified by the method of claim 35.